NATURAL DEATH AND THE DURATION OF LIFE

By Dr. JACQUES LOEB
THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

I

THE efforts to prolong life have resulted in a diminution of the chances of premature death. Nations with adequately developed facilities for medical research and an efficient public health service have practically eliminated smallpox and typhoid, yellow fever and malaria, and have conquered rabies, diphtheria, tetanus, and cerebrospinal meningitis. If this development continues to receive the support it deserves, the time is bound to come when each human being can be guaranteed with a fair degree of probability a full duration of life. But why must we die?

The French encyclopedists of the eighteenth century defined life as that which resists death. What they meant by this definition was the fact that as soon as death sets in, the body begins to disintegrate. They argued correctly that the forces of disintegration were inherent in the living body but were held in check during life. Recent progress in physical chemistry permits us to state that the spontaneous disintegration of the body which sets in with death (at the proper temperature and proper degree of moisture) is a process of digestion, comparable to that which the meat we eat undergoes in our stomach and intestine. The essential feature of digestion is in this case the transformation of the solid meat into soluble products by two ferments, pepsin, which exists in the stomach, and trypsin, which exists in the intestine. The successive treatment of meat by the two ferments results in the breaking-up of the large insoluble molecules into the small soluble molecules of amino acids which are absorbed by the blood and carried to the cells of the body where they are utilized to build up new solid cell matter.

These two ferments, pepsin and trypsin, exist not only in the digestive organs, but in many, and possibly in all living cells, and the question arises, why they do not constantly digest and thus destroy our body while life lasts. A tentative answer

to this question has been given by Dernby, who has been able to show that the cooperation of both ferments is required in the same cell for the work of destruction, and that this cooperation of both ferments becomes possible only at a certain degree of acidity, which cannot be reached in the living body on account of the constant removal of acid through respiration and oxidation. When respiration ceases, the degree of acidity necessary for the digestive action of both ferments in the same cell is reached, leading to gradual digestion and liquefaction of the tissues which characterizes the disintegration of the dead body.

This is not the only cause of disintegration, since the dead body becomes also the prey of the destructive action of microorganisms from the air and in the intestine. During life these same microorganisms are powerless in their attack on the cells protected by a normal membrane, but after death this membrane is destroyed and the action of microorganisms can superimpose itself on that of digestion. It is also probable that the normal secretions of the mucous membranes during life have a protective effect.

Death, then, in a human being means the permanent cessation of respiration. We know that this result can be brought about by mechanical violence, by poison, and by disease, and, since nobody can escape all these agencies, doubts have arisen whether we do not all die from injury or disease, and whether such a thing as natural death really exists. If there were no natural death it should be possible to prolong life indefinitely if a complete protection against disease and accidents could be secured. It is impossible to make such an experiment in a human being, since our intestine and our respiratory tract can not be kept free from microorganisms. The problem has, however, been solved for certain insects. A Russian author, Bogdanow, invented a method of obtaining the common housefly free from all microorganisms, by putting the newly laid eggs for a number of minutes into a solution of bichloride of mercury of sufficient concentration. Most eggs were killed in the process, but some survived and these were free from microorganisms at their surface. By keeping the eggs on sterilized meat and in sterile flasks, the maggots leaving the egg could find their food and develop into flies. A French author, Guyénot, continuing the experiments on the fruit fly, raised 80 successive aseptic generations, and Northrop and the writer have raised thus far 87 aseptic successive generations of the

fruit fly on aseptic yeast. In these experiments all possibility of infection, all chances of accidental or violent death were excluded. To make sure that these flies are absolutely free from microorganisms, their dead bodies are transferred to culture media such as are used for the growth of bacteria. If a common fruit fly is put on such a culture medium, in 24 hours a rapid growth of microorganisms develops, while the culture medium on which our aseptic flies were put remained free from all growth for years (or rather permanently). Aseptic fruit flies, free from infectious disease and supplied with proper food will, therefore, not escape death. These experiments, then, indicate that higher organisms must die from internal causes even if all chance of infection and all accidents are excluded.

II

These aseptic flies served as a means for testing an idea concerning the duration of life which presented itself, namely, that old age and natural death are due either to the gradual production in the body of a sufficient quantity of harmful or toxic substances, or to the gradual destruction of substances in the body required to keep it in youthful vigor, or to both. On this basis the natural duration of life would be in reality the time required to complete a chemical reaction or a series of chemical reactions, resulting in the production of toxic compounds in a quantity sufficient to kill, or resulting in the destruction of necessary compounds. Metchnikoff had called attention to the fact that toxic substances were formed in the intestines under the influence of microorganisms. The intestine of aseptic flies is free from microorganisms, so that the source for the shortening of life pointed out by Metchnikoff need not be considered in this case. The toxic substances formed might be substances formed in one or several organs of the body during their normal activity. Modern physical chemistry furnishes the means of testing such an idea. The period of time required to complete a chemical reaction diminishes rapidly when the temperature is raised and increases rapidly when the temperature is lowered. Exeriments show that the time required for the completion of a chemical reaction is doubled or trebled when the temperature is lowered by 10° centigrade. This influence of temperature upon the rate of processes of nature seems to be typical for chemical reactions. If, therefore, the duration of life is the time required for the completion of certain chemical reactions in the body we might

expect that the duration of life will be doubled or trebled when we lower the temperature ten degrees centigrade. Such experiments can be carried out only in organisms where accidental death by infection is excluded and our aseptic fruit flies satisfied this condition. These experiments were made by Dr. Northrop and the writer, and consisted in putting a number of newly laid eggs of aseptic flies on an abundance of sterilized yeast (which is their natural food) in a flask plugged with cotton. These flasks were put into incubators the temperature of which was kept constant within 0.2 of a degree centigrade. The temperatures selected for the purpose were 10, 15, 20, 25, 27.5, and 30° C. It is not possible to go into the numerous precautions which it was necessary to take and the many technical difficulties involved in this investigation. The result of a large number of experiments was that the duration of life of such aseptic flies was a definite one for each temperature, which means that all the flies died at practically the same age when kept at the same temperature. Thus, for instance, the total average duration of life of such flies was 21.15 days at 30° C. The overwhelming majority died at that age, but a few died a little earlier and a few a little later. When the number of flies of a culture which die on successive days is plotted in terms of percentage of the original number of flies, we get that curve of death rates usually given in life insurance statistics. But this curve is very steep in our case owing to the fact that the majority of flies die at about the same time for a given constant temperature. The following table gives the average duration of life of the fly in days for different temperatures.

TABLE I

Temperature, °C.	Average Duration of Life of the Fly from Egg to Death, Days
30	21.15
25	38.5
20	54.3
15	123.9
10	177.5 + x

This table shows that the influence of temperature on the duration of life of the fly is the same as the influence of temperature on the velocity of a chemical reaction, inasmuch as a lowering of the temperature by ten degrees results in an increase in the duration of life by two or three hundred per cent., and the same figure would be obtained if we investigated the effect of temperature upon the time required to complete a chemical reaction. At 30° C. the flies live on an average 21.15

days and at 20° C. they will live on an average 54.3 days or a little over twice as long. At 25° they live 38.5 days and at 15° C. 123.9 days or about three times as long. The fruit fly is a tropical organism and 30° C. is not far from the optimal temperature. By lowering their temperature twenty degrees we prolong the duration of their life by nine hundred per cent. We cannot lower the temperature below 10° since the flies suffer in the chrysalid stage when the temperature becomes 10° or less. While these are thus far the only experiments on the duration of life of higher organisms carried out with the necessary scientific precaution, there are many casual observations mentioned in the literature which suggest that lowering the temperature prolongs the duration of life of lower animals in general.

The body temperature of a normal human being is constant, namely about 35.5° C. and this temperature remains the same in the tropics and in the arctic regions. Human beings and most mammals differ in this respect from insects whose temperature is as a rule practically that of their surroundings. If if were possible to reduce the temperature of human beings and if the influence of temperature on the duration of life were the same as that in the fruit fly, a reduction of our temperature from 37.5 to about 16° would lengthen the duration of our life to that of Methusaleh; and if we could keep the temperature of our blood permanently at 7.5° C., our average life would (on the same assumption) be lengthened from three score and ten to about 27 times that length, *i.e.*, to about nineteen hundred years. Unfortunately our body does not tolerate any considerable lowering of its temperature and if it did, life at so low a temperature would probably become very monotonous and uninteresting since in all probability sensations of pleasure as well as pain, of joy and of sadness, would be at a very low level.

The experiments on aseptic flies therefore lend support to the idea that the duration of our life is the time required for the completion of a chemical reaction or a series of chemical reactions. If these reactions consist in the gradual accumulation of harmful products in our body, or in the gradual destruction of substances required for a youthful condition, we understand why senile decay and death are the natural result of life.

III

Unicellular organisms, like bacteria, algæ or infusorians, seem to be immortal. They reach a certain size, divide into

two, each half growing again to full size and dividing again, and so on. In this case we may say that it is practically the same individual which continues to live in the successive generations. Small pieces of a cancerous tumor can be transplanted successfully to other individuals and these pieces grow again to a large size. This process can also be repeated indefinitely, and it is the same cancer cell which continues to live in these successive transplantations, as it is the same bacterium which continues to live in successive generations. In this way it has been shown that cancers in mice may outlive many times the natural life of a mouse, in fact they seem to live indefinitely. Cancer cells may therefore be called immortal as was pointed out by Leo Loeb many years ago.

It seems that this is true also for certain normal cells like connective tissue cells. Carrel has isolated connective tissue cells from the heart of a chick embryo and cultures of these cells living on the extracts from chick embryos have been kept alive now for seven years.

All this points to the idea that death is not inherent in the individual cell, but is only the fate of more complicated organisms in which different types of cells or tissues are dependent upon each other. In this case it seems to happen that one or certain types of cells produce a substance or substances which gradually become harmful to a vital organ like the respiratory center of the medulla, or that certain tissues consume or destroy substances which are needed for the life of some vital organ. The mischief of death of complex organisms may then be traced to the activity of a black sheep in the society of tissues and organs which constitute a complicated multicellular organism.

IV

While in human beings there is no sharp limit between youth and maturity, in many insects and amphibians this limit is marked by a sudden metamorphosis in the shape of their body. The frog hatches from the egg as a tadpole without legs and with a long tail. After a certain length of time legs begin to grow, the tail disappears, the form of the head and mouth change, the skin looks different, and the tadpole is transformed into a frog. It is possible that some of the changes underlying metamorphosis are due to changes in the circulation of the blood. Gudernatsch made the remarkable discovery that this metamorphosis, which in our climate usually occurs during the third or fourth month of the life of the tadpole, can be brought

about at will even in the youngest tadpoles, by feeding them with thyroid gland, no matter from which animal. By feeding very young tadpoles with this substance, frogs not larger than a fly could be produced. Allen added the observation that if a young tadpole is deprived of its thyroid gland, it is unable ever to become a frog; and that it remains a tadpole which can reach, however, a long life and continue to grow beyond the usual size of the tadpole. When, however, such superannuated tadpoles are fed with thyroid they promptly undergo metamorphosis. These observations cleared up an old biological puzzle. Salamanders also go through a metamorphosis which is, however, less striking than that of the tadpole of a frog. In the salamander the metamorphosis consists chiefly in the throwing off of the gills, and in changes in skin and tail. In Mexico a salamander occurs which through its whole life maintains its tadpole form, namely the axolotl. Attempts to induce the axolotl to metamorphose failed until after Gudernatsch's discovery an investigator fed the axolotl thyroid gland, and this brought about metamorphosis. The thyroid gland stores the traces of iodine taken up in our food and it seemed possible that the iodine contained in the thyroid was the active principle causing metamorphosis in tadpoles. This was confirmed by Swingle who succeeded in inducing metamorphosis in tadpoles by feeding them with traces of inorganic iodine. According to our present knowledge, the duration of the tadpole stage seems to be the time required to store the necessary amount of certain compounds, one of which contains iodine.

Insects, like the fruit fly, hatch from the egg as maggots which grow at the expense of the food they take up and which, at a certain age, metamorphose into a chrysalid; and from this chrysalid at a given time will rise the winged fly. Feeding of thyroid to the maggots of the fruit fly will not accelerate their metamorphosis, and we can not yet tell whether in this case metamorphosis is due to the accumulation or formation of a definite compound in the body, though this may well be the case. The idea presented itself whether the duration of the larval or maggot stage was not also determined by the temperature (provided the food supply was adequate). We measured, therefore, the influence of temperature upon the duration of the larval state in aseptic fruit flies—*i.e.*, from the time the egg was laid until the maggot was transformed into a chrysalid. The influence was practically identical with that of temperature on the total duration of life. Thus the larval period lasted 5.8 days at

25° C. and 17.8 days at 15° C., a ratio of about 1:3. The total duration of life of aseptic flies is 38.5 days at 25° and 123.9 days at 15° C., also a ratio of about 1:3. We are, therefore, justified in making the statement that the influence of temperature upon the duration of the larval period or the youth of aseptic flies is practically identical with the influence of temperature on the total duration of life.

Experiments by Uhlenhuth on the influence of temperature on metamorphosis in salamanders have shown that it is similar to that observed in flies. Salamanders kept at 25° metamorphosed when they were 11 weeks old, while salamanders kept at 15°, under otherwise identical conditions, metamorphosed when they were 22 weeks old. All these data suggest the possibility that the duration of life and the duration of the larval period or of youth are in reality times required for the completion of definite chemical reactions. The cessation of respiration leading to the termination of life and the alterations in circulation leading to metamorphosis or termination of youth are critical points; and it seems possible that these points are reached when a certain toxic substance is formed in adequate quantity in the body, or when a necessary substance is destroyed or sufficiently diminished in quantity, or when both conditions are fulfilled.

We can prolong or shorten the period of youth in amphibians not only by modifying the temperature but by withdrawing or offering the specific substance which causes metamorphosis, namely iodine or thyroid material. There is no end to the substances capable of hastening death. Shall we ever find a substance which will prolong the duration of life? At present we can neither deny nor affirm the possibility.